Cardiovascular Consequences of Weightlessness Promote Advances in Clinical and Trauma Care

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Abstract: Cardiovascular adaptations driven by exposure to weightlessness cause some astronauts to experience orthostatic intolerance upon return to Earth. Maladaptations of spaceflight that lead to hemodynamic instability are temporary, and therefore astronauts provide for researchers a powerful model to study cardiovascular dysfunction in terrestrial patients. Orthostatic intolerance in astronauts is linked to changes in the autonomic control of cardiovascular function, and so patients that suffer neurocardiogenic syncope may benefit from a greater understanding of the effects of spaceflight on the autonomic nervous system. In addition, appropriate autonomic compensation is fundamental to the maintenance of stable arterial pressures and brain blood flow in patients suffering traumatic bleeding injuries. The application of lower body negative pressure (LBNP), an experimental procedure used widely in aerospace physiology, induces autonomic and hemodynamic responses that are similar to actual hemorrhage and therefore may emerge as a useful experimental tool to simulate hemorrhage in humans. Observations that standing astronauts and severely injured patients are challenged to maintain venous return has contributed to the development of an inspiratory impedance threshold device that serves as a controlled "Mueller maneuver" and has the potential to reduce orthostatic intolerance in returning astronauts and slow the progression to hemorrhagic shock in bleeding patients. In this review, we focus on describing new concepts that have arisen from studies of astronauts, patients, and victims of trauma, and highlight the necessity of developing the capability of monitoring medical information continuously and remotely. Remote medical monitoring will be essential for long-duration space missions and has the potential to save lives on the battlefield and in the civilian sector.

Key Words: Microgravity; autonomic nervous system; orthostatic intolerance; combat casualty care; hemorrhagic shock

INTRODUCTION

Astronaut as a Model

Humans have been making sojourns to the microgravity environment of space for a half century. Contrary to early predictions of catastrophic cardiovascular insufficiency during flight, the absence of gravitational acceleration seems to simply redefine "normal" cardiovascular function [1], and hemodynamic regulatory mechanisms adapt appropriately to maintain adequate systemic oxygenation and organ function. It is only when astronauts return to Earth and are once again exposed to hydrostatic gradients that adaptations occurring in space manifest as cardiovascular deficiencies. Microgravity exposure decreases exercise capacity [2], and 40% to 50% of astronauts returning from space cannot stand passively for 10 minutes [3-5] without experiencing symptoms of impending syncope such as hypotension, lightheadedness, and/or tunnel vision. Postflight orthostatic intolerance could potentially put astronauts at risk in the event that an emergency necessitates rapid evacuation from a space vehicle upon landing, and therefore the National Aeronautics and Space Administration (NASA) has placed a priority on uncovering mechanisms underlying postflight orthostatic intolerance so that effective countermeasures may then be implemented.

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Wally Schirra, the first American astronaut to report an experience of postflight orthostatic instability, flew over forty years ago. Since that time, various countermeasures have been tested but none have been found to be wholly effective. The absence of effective countermeasures could potentially put astronauts at risk; however, approximately 430 people have been to space since the flight of Yuri Gagarin, and the specter of catastrophic safety hazards relating to reduced exercise capacity and orthostatic instability has not materialized. In fact, it could be argued that postflight orthostatic instability and cardiovascular deconditioning are little more than temporary inconveniences. The real benefit of understanding underlying mechanisms of post-flight orthostatic intolerance may not be the development of countermeasures for astronauts, but may instead be the application of knowledge gained to address a number of other more serious problems for people on Earth.

For example, unexplained syncope is a debilitating condition for many otherwise normal, healthy people, and accounts for approximately 3% of all emergency room visits [6]. Prolonged bedrest prescribed for any number of reasons also causes cardiovascular deconditioning similar to that seen in astronauts. Delays in reambulation after prolonged bedrest could compromise rehabilitation. Countermeasures or therapeutic procedures designed to help astronauts may transfer well to clinical treatment and rehabilitation of syncopal patients. In addition to physiological links to clinical problems, problems associated with post-flight orthostatic intolerance, specifically the inability to maintain adequate stroke volume and cardiac output, are similar to life-

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threatening problems experienced by patients suffering traumatic bleeding injuries. Lessons learned from space are driving research in trauma care and have the potential to save lives.

Cardiovascular adaptations to spaceflight are temporary, and therefore astronauts provide a unique model to address serious problems. Astronauts who are otherwise healthy before they go to space may be made "sick" by simply removing gravitational acceleration, and then returned to health once their cardiovascular systems readapt to 1-G. In this review, we provide a general overview of cardiovascular adaptations to spaceflight and highlight potential mechanisms underlying post-flight orthostatic intolerance. We discuss briefly countermeasures and experimental procedures that have been developed for returning astronauts and their potential use in a clinical setting. We conclude by addressing similarities between research on astronauts and potential applications for trauma patients requiring immediate life saving interventions, and we discuss the implications of autonomous medical monitoring as a necessary next step for spaceflight, civilian trauma, and combat casualty care.

CARDIOVASCULAR ADAPTATIONS TO SPACEFLIGHT

Headword Fluid Shifts and Blood Volume

It is well established that upon entry into microgravity astronauts experience a cephalad shift of fluid resulting in facial puffiness and distended neck veins. This headword fluid shift causes distention of cardiac chambers [7-8], which in turn activates mechanisms associated with rapid blood volume reduction (~12% to 15% within 48 hours of initial microgravity exposure [9-11]). The mechanisms underlying in-flight diuresis have not been determined, and post-flight orthostatic intolerance cannot be explained exclusively by reduction of blood volume. For example, astronauts return from space with blood volume reductions of similar magnitudes to that of blood donors on Earth, but blood donation only rarely leads to fainting episodes [12]. Although fluid loading of astronauts prior to reentry may improve orthostatic stability for short duration missions of 3 to 5 days [13], fluid loading appears ineffective in alleviating symptoms of impending syncope in spaceflights that last longer than 7 days [3, 14].

Autonomic Neural Adaptations

Upright standing displaces blood from the chest toward the legs, causing stroke volumes and pulse pressures to decrease. As pulse pressures narrow, arterial distention is less, and therefore arterial baroreflexes are effectively unloaded resulting in withdrawal of parasympathetic, and activation of sympathetic efferent neural traffic. Effective autonomic reflex compensations result in increases in heart rate and peripheral vascular resistance and help defend against decreases in arterial pressure. Orthostatic hypotension occurs in humans with pathological baroreceptor denervation [15] and in animals after experimental baroreceptor denervation [16], revealing that arterial baroreflex function is essential to maintenance of stable arterial pressures during orthostasis. Using 6^0 head down bedrest as a ground-based analog of microgravity, Convertino *et al*. [17] documented reduced carotid-cardiac baroreflex responsiveness by day 12 of a 30 day bedrest protocol, and on day 30, 4 of the 10 subjects could not stand unaided for five minutes. Subjects with the greatest decline in carotid baroreflex function also experienced the greatest decline in systolic pressure upon standing post bedrest [17]; this observation led to the hypothesis that actual spaceflight would reduce the responsiveness of the carotid-cardiac baroreflex, and that such reductions would contribute to post flight orthostatic intolerance. Two subsequent studies confirmed that carotid-cardiac barororeflex function is reduced after short-term (4 to 5 days [18] and 8 to 14 days [19]) space flight. In addition to tests of carotid-cardiac baroreflex responses in the study by Fritsch-Yelle *et al*. [19], astronauts also performed Valsalva maneuvers to explore the effects of spaceflight on non-specific baroreflex function. The magnitude of increase in R-R interval for a given increase in systolic pressure during phase IV of the Valsalva maneuver (with phases identified as originally outlined by Hamilton *et al*. [20]) was less in astronauts post-flight compared to pre-flight. In agreement with the earlier bedrest studies of Convertino *et al*. [17], astronauts with the greatest reduction of baroreflex function also had the greatest reduction of systolic pressure during post-flight stand tests (19).

The effects of duration of exposure to microgravity on arterial baroreflex function are largely unknown. Cooke *et al*. [21] studied baroreflex sensitivities of three Russian cosmonauts during two separate nine-month missions to the Russian space station Mir. Integrated baroreflex responses (assessed in the frequency domain with transfer function analysis between systolic pressures and R-R intervals) were reduced in-flight by about 25% in one cosmonaut at day 18. In two others, baroreflex sensitivity was similarly reduced by about 25% at days 120 and 180. After returning from nine months in space, baroreflex sensitivity was reduced by half for one cosmonaut one day post-flight and for two others 14 days postflight [21]. Although there are not sufficient data to propose that baroreflex function changes as a function of mission duration, Meck *et al*. [22] reported greater incidences of orthostatic intolerance during post-flight stand tests in astronauts after long- compared to short-duration missions, suggesting that the magnitude of microgravity-induced adaptations leading to post-flight orthostatic intolerance may depend on the duration of exposure to microgravity.

Reduction of vagal baroreflex sensitivity could limit the adequacy of heart rate responses to changes in arterial pressure and contribute to orthostatic intolerance. Adequacy of sympathetic responses to orthostasis is similarly important. Sympathetic nerves fire and increase vascular resistance in response to reductions of arterial blood pressure [23], but only within a finite range of pressures [24]. Once sympathetic activation is maximal, further reductions of arterial pressure cause parallel reductions of both arterial pressure and sympathetic nerve activity [25-27]. The effects of spaceflight on the sympathetic nervous system have not been studied thoroughly, although associations among changes occurring in sympathetic activity in-flight and sympathetic responses to standing post-flight are beginning to emerge. Plasma catecholamines have been shown to be increased [28, 29], unchanged [30], or decreased [31] in-flight. Data from

the last dedicated Spacelab mission onboard the American Space Shuttle (Neurolab, STS-90) indicated increased sympathetic activity in space as assessed directly from the peroneal nerve with the microneurography technique and from plasma norepinephrine spillover and clearance [32]. Neurolab astronauts returned from space with elevated supine sympathetic activity, and increased their sympathetic traffic more post-flight compared to pre-flight during passive tilt testing [33]. Increased sympathetic responses to standing seemed to be appropriate for reduced stroke volumes both supine and during tilt post-flight, and no astronaut experienced symptoms of pre-syncope [33]. Lack of a positive tilt test coupled with appropriate sympathetic activation post-flight in the Neurolab astronauts (n = 5) does not rule out sympathetic adaptations as potential mechanisms underlying post-flight orthostatic intolerance. Inadequate sympathetic activation during stand tests post-flight has been implicated previously [3, 34].

Mechanisms underlying orthostatic instability are not ubiquitous and must be considered in light of individual susceptibilities. Susceptibility to orthostatic intolerance has been linked to both hypo- [4, 34] and hyper-adrenergic [35-37] responses to standing or tilting, or to simulated orthostatic stress with lower body negative pressure [27]. The concept of a "sympathetic threshold" supports the notion that maximal sympathetic activation is followed by abrupt sympathetic withdrawal when either arterial pressures or cardiac filling falls below some threshold level [25-27]. The upper two panels of Fig. (**1**) show arterial pressure and muscle sympathetic neural activity from one subject who tolerated without incident 10 minutes of -60 mmHg chamber decompression in an LBNP device (non susceptible subject). Note that arterial pressures oscillate, and that when pressures decrease sympathetic traffic increases. The subject depicted in the upper panels of Fig. (**1**) displays a normal sympathetic baroreflex response with normal periods of activation and inhibition. In contrast, the subject depicted in the lower panel of Fig. (**1**) arguably has no arterial pressure oscillations and sympathetic traffic has been maximized during the period prior to cardiovascular collapse. We suggest that at this point the subject has reached a sympathetic threshold where further increases in sympathetic traffic are not possible. Arterial pressure begins to decline along with sympathetic traffic to the point of abrupt hypotension occurring in conjunction with total sympathetic neural withdrawal.

In this context, it could be that those astronauts with adequate sympathetic reserves are better able to compensate for orthostatic stress, while those astronauts who maximally activate sympathetic traffic upon standing may not be able to defend against hypotension when they return from space

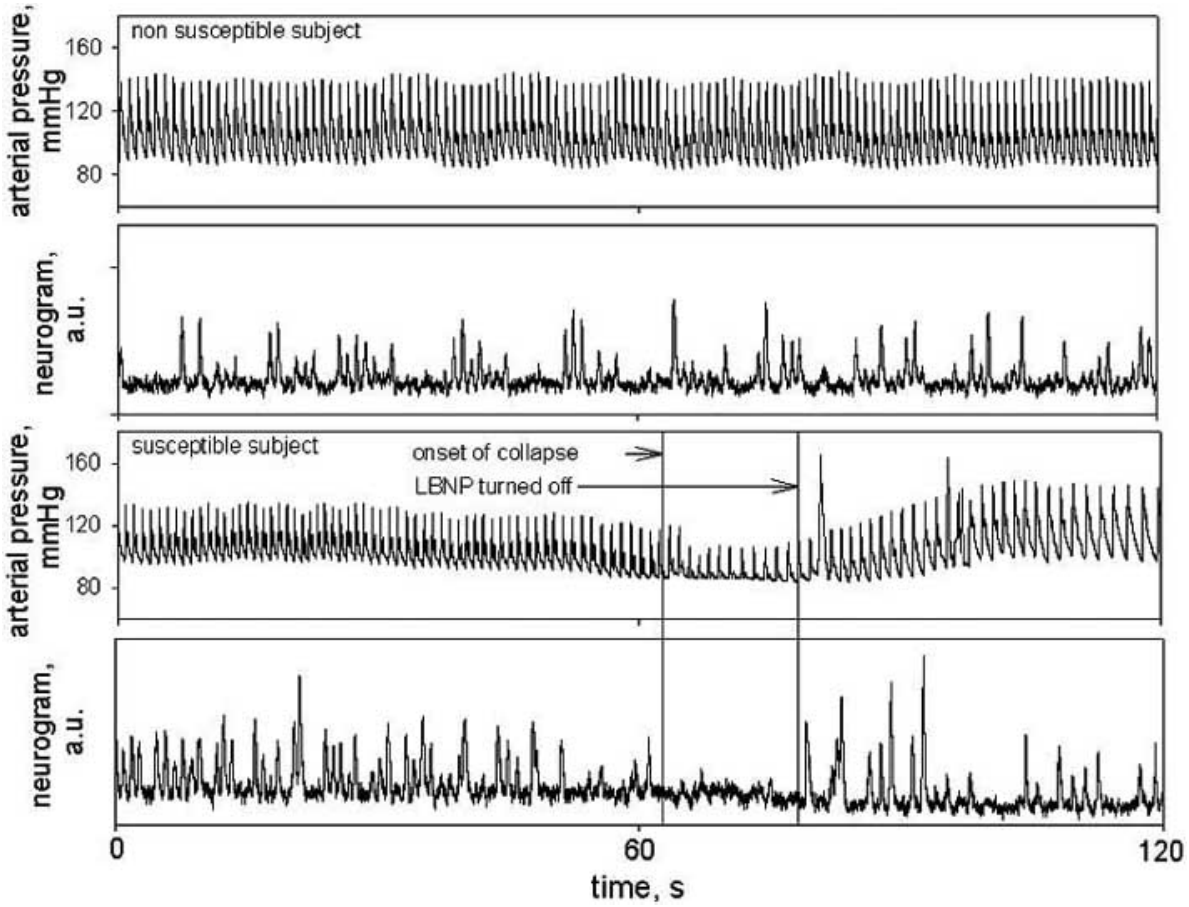

Fig. (1). Arterial pressures and muscle sympathetic nerve activities are shown for one subject who tolerated 10 minutes of 60 mmHg LBNP (non susceptible subject) and for one subject who experienced symptoms of hemodynamic instability (susceptible subject) at 60 mmHg LBNP. Figure reproduced from [27].

with reduced blood volumes. Due to small sample sizes inherent in space physiology research, it is not possible at this time to attribute post-flight orthostatic intolerance to adaptations in either branch of the autonomic nervous system, but understanding such autonomic adaptations in conjunction with re-adaptation to 1-G has contributed to a better understanding of neurocardiogenic syncope and other serious autonomic problems for people on Earth.

Cardiac Structural and Functional Adaptations

Echocardiographic measurements obtained in astronauts before and after space flight missions revealed 8% to 12% reductions in left ventricular dimensions [8, 38, 39]. More recent use of magnetic resonance imaging revealed an average 14% reduction in the left ventricular mass of four astronauts following their 10-day mission, supporting the hypothesis that the smaller cardiac size observed after space flight reflected atrophy of myocardial muscle [40]. Contrary to the notion of myocardial atrophy, recent evidence generated from ground-based and flight experiments on animals suggests that smaller myocardial mass may reflect simply the impact of negative caloric balance and body mass routinely observed in astronauts during space flight [41]. Since the loss of body fluids represents a significant amount of body mass reduction in astronauts, it is possible that the apparent reduction in cardiac size represents a loss in tissue water rather than muscle atrophy. This hypothesis is consistent with the observations that there is little impact of exposure to microgravity on cardiac function obtained from various non-invasive measures such as end-diastolic volume-stroke volume curves, ejection fractions, and arterial pulse wave velocities during rest and exercise [2, 38, 39, 42].

Vascular Adaptations

Vascular smooth muscle undergoes structural autoregulation in response to changes in vessel wall tension and shear stress [43], and it is therefore reasonable to speculate that translocation of fluid volumes from the lower to the upper body in microgravity would stimulate vascular remodeling. In experiments conducted on 14 astronauts following 9-14 days of space flight, Buckey and co-workers [3] reported that astronauts who failed to complete 10 minutes of standing after return from their mission displayed a smaller elevation in peripheral vascular resistance than orthostatically-stable crew members. This relationship between low vascular resistance and failure to complete stand tests has been corroborated in an additional 40 astronauts after spaceflight [34]. An association between blunted reflex vasoconstriction and low circulating norepinephrine in astronauts following their space mission has been used to promote the hypothesis that a hypoadrenergic responsiveness contributes to post-flight orthostatic intolerance [4]. However, comparisons of NE analyzed from blood samples drawn from presyncopal astronauts after they returned to the supine position with samples drawn from non-presyncopal astronauts in the upright posture make the interpretation of low norepinephrine and attenuated vascular resistance tenuous at best. Other evidence suggests that exposure to microgravity may cause alterations at the site of vascular smooth muscle that might limit vasoconstriction after space flight such as increased vascular beta-adrenoreceptor (vasodilatory) sensitivity [44], decreased vascular alpha-adrenoreceptor (vasoconstrictor) sensitivity [5], atrophy and reduced contractile force of vascular smooth muscle [45], lower vasoreactivity [45, 46], and/or perivascular hypoinnervation [46].

Both spaceflight [47] and groundbase [48] experiments have provided evidence that baseline (resting) vascular resistance is increased after exposure to microgravity. Increased peripheral vasoconstriction reflects a sympathetically-mediated reflex compensatory response to a reduction in vascular volume, stroke volume and cardiac output. In one investigation, average stroke volume in 6 astronauts decreased from approximately 135 ml during supine rest to 75 ml during 70° head-up tilt prior to space flight [33]. Following space flight, the magnitude of reduction in stroke volume during tilt was similar in these same astronauts, but had shifted so that average stroke volume decreased from 105 ml in supine rest to 45 ml during tilt. A linear relationship between increased muscle sympathetic nerve activity and stroke volume was maintained between pre- and post-space flight tilt tests, suggesting a tight coupling (signaling) between stroke volume and sympathetically-mediated reflex responses. Since maximal vasoconstriction is finite, an elevated resting vasoconstriction represents a reduction in the reserve to vasoconstrict peripheral vessels and subsequently lowers the capacity to buffer against the development of orthostatic hypotension [49].

Whether peripheral vascular adaptation to microgravity involves hypoadrenergic responsiveness, alterations in adrenoreceptor function, atrophy and reduced contractile force of vascular smooth muscle, lower vasoreactivity, perivascular hypoinnervation, and/or reduced vasoconstriction reserve, gaining new insight and understanding of how these mechanisms contribute to cardiovascular collapse in presyncopal astronauts in a hypovolemic state can prove critical to the development of effective treatment(s) of circulatory shock as well as orthostatic intolerance.

ADVANCES IN CLINICAL AND TRAUMA CARE

Syncope

Humans on Earth contend daily with hydrostatic pressure gradients that threaten the ability to maintain an upright posture. With the transition from a supine to upright position, fluid shifts from the thorax to the dependent regions of the lower body are counteracted by intrinsic feedback mechanisms designed to maintain adequate venous return and cerebral perfusion. When these compensatory mechanisms fail, arteries may dilate, cardiac outputs may fall, and mean carotid arterial pressures may drop below 70 mmHg. If carotid pressures are maintained around 70 mmHg for longer than about 10 seconds, cerebral autoregulatory mechanisms may malfunction leading to loss of consciousness and postural integrity (syncope) [50, 51]. Although the etiology of syncope is not understood completely, most syndromes include a neural component and have been classified in general as neurally mediated (or neurocardiogenic) syncope. Of the different forms of neurocardiogenic syncope observed clinically, at least two - vasodepressor syncope and vasovagal syncope - appear to most closely match patterns of orthostatic failure experienced by returning astronauts [3, 52]. For example, in a majority of astronauts who could not com-

plete a 10 minute stand test [3], arterial pressures fell progressively despite maintained heart rates as seen with vasodepressor syncope. In one other astronaut who experienced post-flight orthostatic intolerance [3], arterial pressure fell abruptly in conjunction with bradycardia as seen with classic vasovagal syncope [50, 52]. Although orthostatic instability in astronauts studied by Buckey and co-workers [3] was linked to an inability to increase peripheral vascular resistance, susceptibility to orthostatic intolerance in astronauts has also been linked to blunted vagal-cardiac reflexes [53]. In this respect, the etiology of orthostatic intolerance is also similar to that of clinical syncope observed in spinal-injured and diabetic patients [54, 55]. However, susceptibility to syncope in Earth-bound patients has also been linked to heightened parasympathetic activity, as assessed indirectly from resting heart rates, heart rate variabilities, and responses to the Valsalva maneuver [56-58].

Lower Body Negative Pressure to Simulate Hemorrhage

Body fluid redistribution from the upper body to the abdomen and dependent regions of the lower body can be induced and controlled in humans by applying negative pressure below the iliac crest. Since the first description of this research tool [59], lower body negative pressure (LBNP) has been used extensively in aerospace research [60, 61]. Astronauts began using LBNP during the Skylab mission and have used LBNP as recently as the Neurolab mission [32] as a means to understand better the complexities of autonomic cardiovascular regulation in a weightless environment. The use of LBNP on Earth as a means to explore autonomic mechanisms is attractive because the procedure provides reproducible responses [60], and because it provides a safe means to bring normal, healthy subjects to the point of pre-syncope. Symptoms of pre-syncope resolve completely and quickly when the vacuum is turned off and fluid once again redistributes toward the heart and head (as suggested by the response of the susceptible subject in the bottom two panels of Fig. (**1**)). Experiments incorporating LBNP have addressed primarily the consequences of hypovolemia on hemodynamic instability and have focused predominantly on understanding physiological adaptations to simulated or actual microgravity [62-81]. We have suggested recently that that LBNP may be useful as a procedure to simulate acute hemorrhage in humans and therefore provide a means to begin to develop algorithms to predict the onset of hemorrhagic shock [60, 82]. Hemorrhage is the primary cause of death on the battlefield [83] and a leading cause of death in civilian trauma [84]. Improving outcomes for patients with traumatic injuries including severe hemorrhage [85, 86] has been targeted as a research area in need of attention by the Post Resuscitative and Initial Utility of Life Saving Efforts (PULSE) working group of the National Institutes of Health [87].

We reviewed previously the available data on hemorrhaging humans and attempted to correlate magnitudes of hemorrhage to magnitudes of LBNP chamber decompression based on compensatory physiological responses [82]. Our best estimates describing this relationship are displayed in Table **1**. We recognize that the LBNP procedure is not a perfect hemorrhage simulation. With LBNP there is no hole in a vessel and so physiological compensations relate specifically to fluid redistribution and not to fluid loss necessarily. With LBNP one does not contend with soft tissue trauma or sepsis common in wounded soldiers or civilians, and LBNP may not induce significant tissue acidosis (although to our knowledge the influence of LBNP on muscle tissue metabolism has not been determined). Nevertheless, physiological compensations to LBNP are remarkably similar to actual hemorrhage as summarized in Table **2**.

Table 1. Classification of Hemorrhage Severity in Humans and Magnitudes of Lower Body Negative Pressure (LBNP)

LBNP	Hemorrhage
10 to 20 mmHg 400 to 550 ml fluid displaced	(Mild) 400 to 550 ml 10% of total blood volume
20 to 40 mmHg 500 to 1000 ml fluid displaced	(Moderate) 550 to 1000 ml 10 to 20% of total blood volume
40 mmHg and up ≥ 1000 ml fluid displaced	(Severe) > 1000 ml > 20% of total blood volume

Hemorrhage data are from humans, and represent approximations and ranges from the literature Definitions of mild, moderate, or severe hemorrhage (in parentheses) correspond to usage in the text Table reproduced from [82]

Heart rate increases progressively with hemorrhage or LBNP until research volunteers or trauma victims experience cardiovascular collapse or hemorrhagic shock. At high levels of LBNP and in response to severe hemorrhage, a relative bradycardia may develop (this is seen in approximately 30% of bleeding patients [88, 89]) which is likely associated with abrupt sympathetic neural withdrawal and vagal activation. Arterial pressures are either maintained or slightly increased with progressive reductions of stroke volume, cardiac output, and central venous pressure until the onset of shock or collapse associated with abrupt hypotension. Either blunted or exaggerated sympathetic activation occurs prior to shock or collapse, but it is probable that in all cases, onset of hypotension occurs in conjunction with sympathetic neural withdrawal [27, 90, 91]. Due to local autoregulation of various vascular beds, evaluation of catecholamines and other vasoactive hormones from plasma samples provides little insight (beyond global responses) into progression to cardiovascular collapse. We feel that it is this progression to trouble that must be better understood. In this regard, LBNP experiments may provide important answers that will help in the development of prediction algorithms that may in the future drive the development of devices capable of increasing the decision options of combat medics or civilian paramedics, and thereby increase the efficiency and effectiveness of triage and treatment.

We evaluated recently the utility of heart rate variability and analysis of integrated baroreflex sensitivity as potential markers that change predictably during simulated hemorrhage using LBNP. Our primary results are shown in Fig. (**2**) [92]. Although it is not surprising that LBNP induces pro-

Table 2. Comparison of Global Physiological Responses to Hemorrhage and LBNP

Classification Hemorrhage LBNP	Stage I (Mild) 10 to 20 mmHg	Stage II (Moderate) 20 to 40 mmHg	Stage II (Severe) > 40 mmHg	Stage III (Shock) Collapse
Variable				
HR	↑ ↔	↑ ↑	↑ ↑	↑↓ ↓
MAP	↔ ↔	↑ ↔	↑ ↑	↑ ↓
SV	↓ ↓	↓ ↓	↓ ↓	↓ ↓
Q_c	↓ ↓	↓ ↓	↓ ↓	↓ ↓
CVP	↓ ↓	↓ ↓	↓ ↓	↓ ↔ ↓ ↔
SNA	↑ ↑	↑ ↑	↑ ↑	↓ ↓
NE	↑ ↑	↑ ↑	↑ ↑ ↔*	↓ ↓
PVR	↑ ↑	↑ ↑	↑ ↑	↓ ↓
AVP	↔ ↔	↔ ↔	↔ ↔ ↑*	NA ↑
PR	↔ ↔	↔ ↔	↔ ↔ ↑*	NA ↑
ANG II	NA ↔	NA ↔	NA ↑	NA ↑
PPH	↔ ↔	↔ ↔	↑ ↑	↑ ↑

Under each condition, variables either increase (↑), decrease (↓), do not change (↔), or show differential responses (↓ ↔; ↔ ↑) Responses to hemorrhage are shown in bold font and responses to LBNP are shown in normal font; NA, data not available or too limited to present; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; Q_c, cardiac output; CVP, central venous pressure; SNA, sympathetic nerve activity; NE, norepinephrine; PVR, peripheral vascular resistance; AVP, arginine vasopressin; PR, plasma renin; ANG II, angiotensin II; PPH, pancreatic polypeptide hormone; (*) asterisk, directional changes only in subjects susceptible to hemodynamic collapse or at the onset of hypotension Table reproduced from [82]

gressive vagal withdrawal, what is often not appreciated is the lack of change in mean arterial pressure even at high levels of LBNP. The results shown in Fig. (**2**) represent mean responses of 13 subjects with appropriate autonomic compensation to induced central hypovolemia. It is likely that many victims of trauma have normal arterial pressures during the period of time their autonomic neural responses to blood loss are appropriate, but that after their status has been determined as "stable" they may progress quickly toward hemorrhagic shock. We propose that measures of autonomic function such as heart rate variability and baroreflex sensitivity as shown in Fig. (**2**) may provide a first responder with the means to more accurately track progression to hemodynamic instability.

When astronauts return from space and stand passively, their stroke volume reductions are greater than those recorded before flight due primarily to reduced blood volumes [33]. Stroke volume is related directly to preload and therefore is potentially an important variable that could be used to estimate the magnitude of blood loss in bleeding patients. The obvious problem is how one would measure stroke volume in the field. It is more reasonable to identify a surrogate measure that relates to stroke volume that is readily obtainable in the field: we suggest that pulse pressure may be that variable. Fig. (**3**) shows progressive reductions of stroke volume and pulse pressure together with increases of muscle sympathetic nerve activity and unchanged arterial pressure as functions of LBNP magnitude. Fig. (**4**) shows the relationship between stroke volume and pulse pressure during LBNP. Because pulse pressure is a function of both volume and vascular distensibility, pulse pressure may not decrease

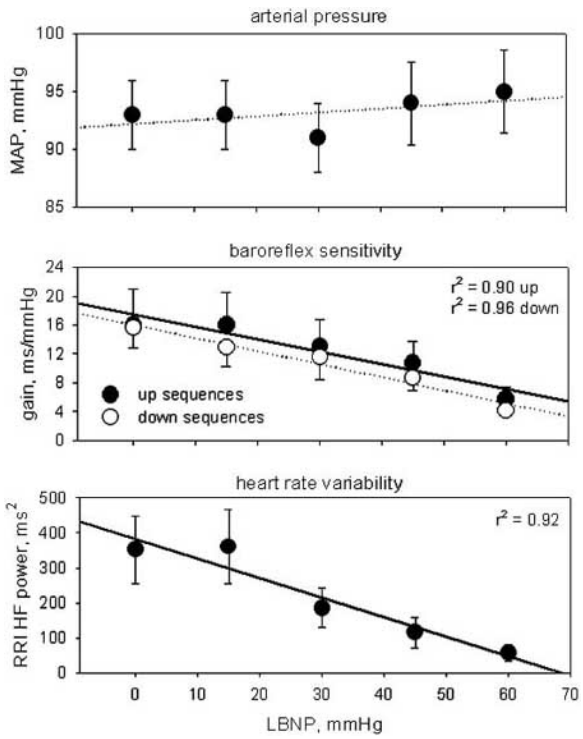

Fig. (2). The effects of progressive central hypovolemia induced by LBNP are shown for mean arterial pressures (MAP), cardiac baroreflex sensitivity of up and down sequences, and integrated R-R interval spectral power at the high frequency [RRI HF power; (0.15-0.4 Hz)]; n = 13. Figure reproduced from [92].

as a simple linear function of LBNP magnitude, but may be described better by a third order regression as shown in Fig. (**4**). With this construct, we speculate that the three components of this model might be blood volume, mechanical properties of smooth muscle, and the degree of norepinephrine-induced vascular tone, but we have not tested this speculation experimentally. Underlying mechanisms notwithstanding, pulse pressures are easily obtained by a first responder with access to a blood pressure cuff. Experiments incorporating LBNP as a hemorrhage simulation could lead to guidelines for use in the field describing ranges of pulse pressures and associated ranges of estimated blood loss.

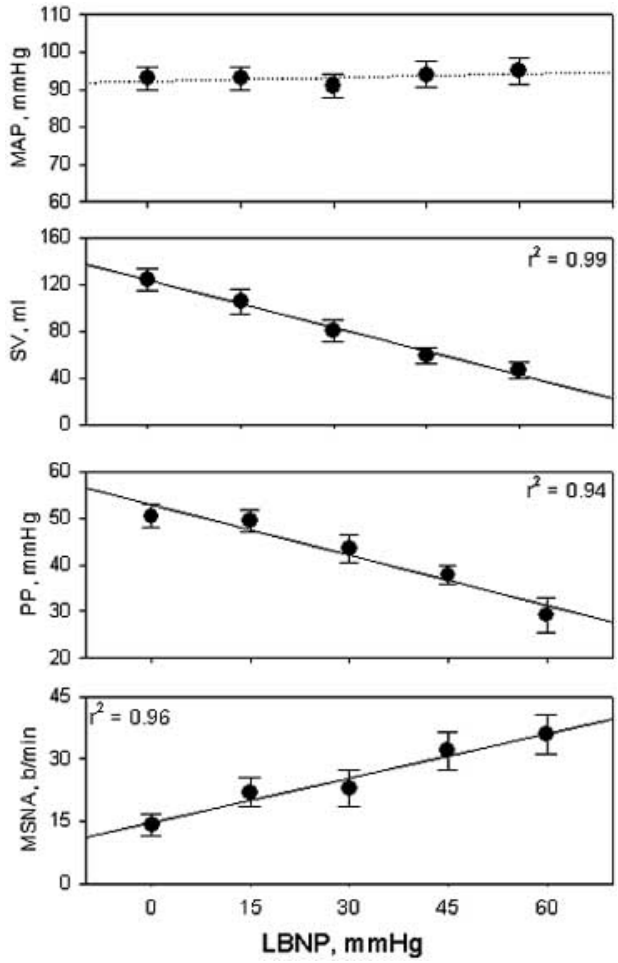

Fig. (3). The effects of progressive central hypovolemia induced by LBNP are shown for mean arterial pressures (MAP), stroke volume (SV), pulse pressure (PP), and muscle sympathetic nerve activity (MSNA); n = 13 for MAP, SV, and PP; n = 10 for MSNA at 0; n = 9 for MSNA at -15 mmHg; n = 6 for MSNA at -30 and -45 mmHg; n = 4 for MSNA at -60 mmHg. Data are unpublished observations from Cooke, W.H. and Convertnio, V.A.

A Promising New Device for the Treatment of Syncope or Shock

Astronauts who experience postflight orthostatic intolerance sit or lie down until they feel better. People who suffer traumatic injuries and lose blood rely on the same physiologic mechanisms as standing astronauts to maintain adequate blood pressures, but at some point compensatory mechanisms are overwhelmed by the magnitude of blood loss and these patients progress to hemorrhagic shock and die in the absence of immediate life saving intervention. For both astronauts and bleeding patients, the key to hemodynamic stability is adequate venous return and cardiac output. If autonomic compensations for reduced venous return are not adequate, it is possible to increase venous return mechanically.

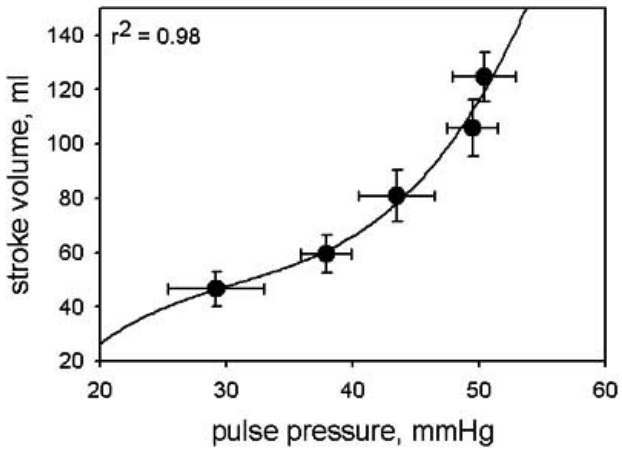

Fig. (4). Stroke volume is plotted as a function of pulse pressure during progressive central hypovolemia with LBNP; n = 13. Data are unpublished observations from Cooke, W.H. and Convertnio, V.A.

A series of animal and human experiments have shown the utility of inspiratory impedance as a mechanical tool to assist in the restoration of central blood volume. When breathing against a resistance, the vacuum effect within the thorax increases during each inspiration. Such negative intrathoracic pressures during resistive breathing have been shown enhance venous return and preload [93-95]. An Inspiratory impedance Threshold Device (ITD) was developed by Advanced Circulatory Systems Inc. (Eden Prairie, MN) which consists of an impedance valve of various cracking pressures (~7 to 12 cmH_2O) attached to a facemask. The ITD is shown in Fig. (**5**).

Breathing through the ITD increased stroke volume, cardiac output and arterial blood pressure in supine human subjects [96, 97]. Importantly, breathing through the ITD reduced total peripheral vascular resistance [96], suggesting an increase in vasoconstrictor reserve. Given that orthostatic intolerance has been linked with an inability to increase peripheral resistance adequately [3], and considering the likelihood of the existence of a sympathetic threshold [25-27], resistive breathing could reduce sympathetic traffic (by loading cardiopulmonary mechanoreceptors) and shift subjects to the right on their sympathetic traffic - arterial pressure relations, effectively increasing their sympathetic reserves. Although the link between decreases of peripheral vascular resistance and decreases of sympathetic traffic during resistive breathing has not been shown definitively, directly recorded muscle sympathetic nerve activity decreased from 30 to 23 bursts/min in one subject breathing on an ITD device [96]. These data are shown in Fig. (**6**).

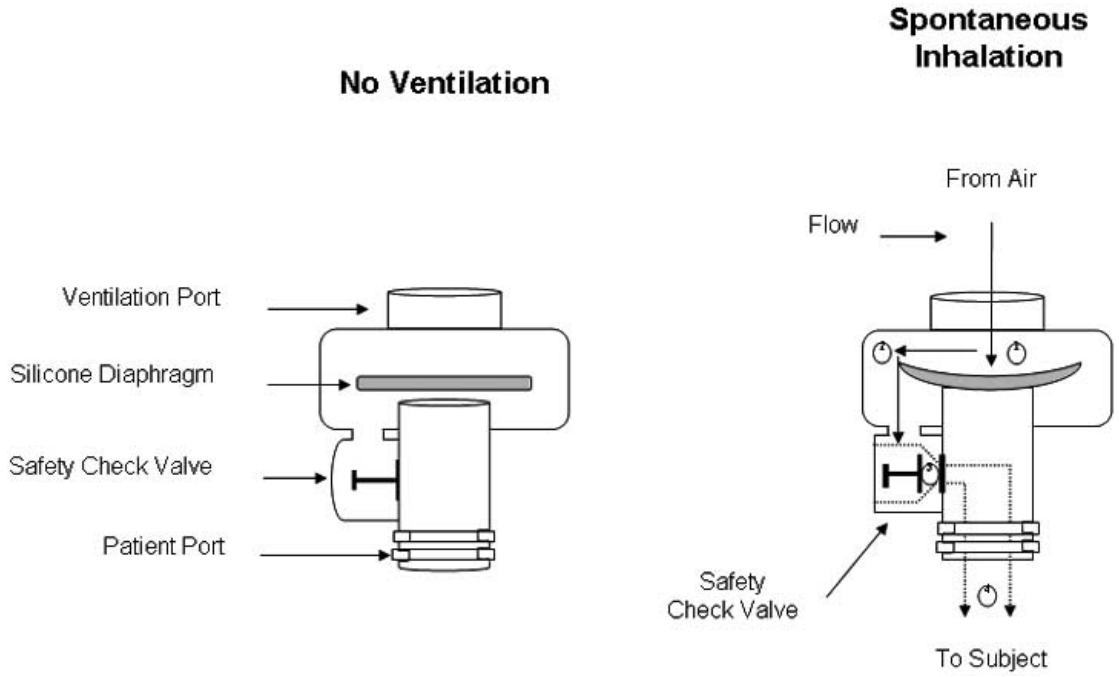

Fig. (5). Drawing illustration of the Impedance Threshold Valve. During spontaneous inspiration, air flow from the ventilation port to the subject causes the silicone diaphragm to close. The air flow bypasses the diaphragm to the Safety Check Valve. When intrathoracic pressure reaches and exceeds the impedance threshold of the valve, the Safety Check Valve opens and air reaches the subject.

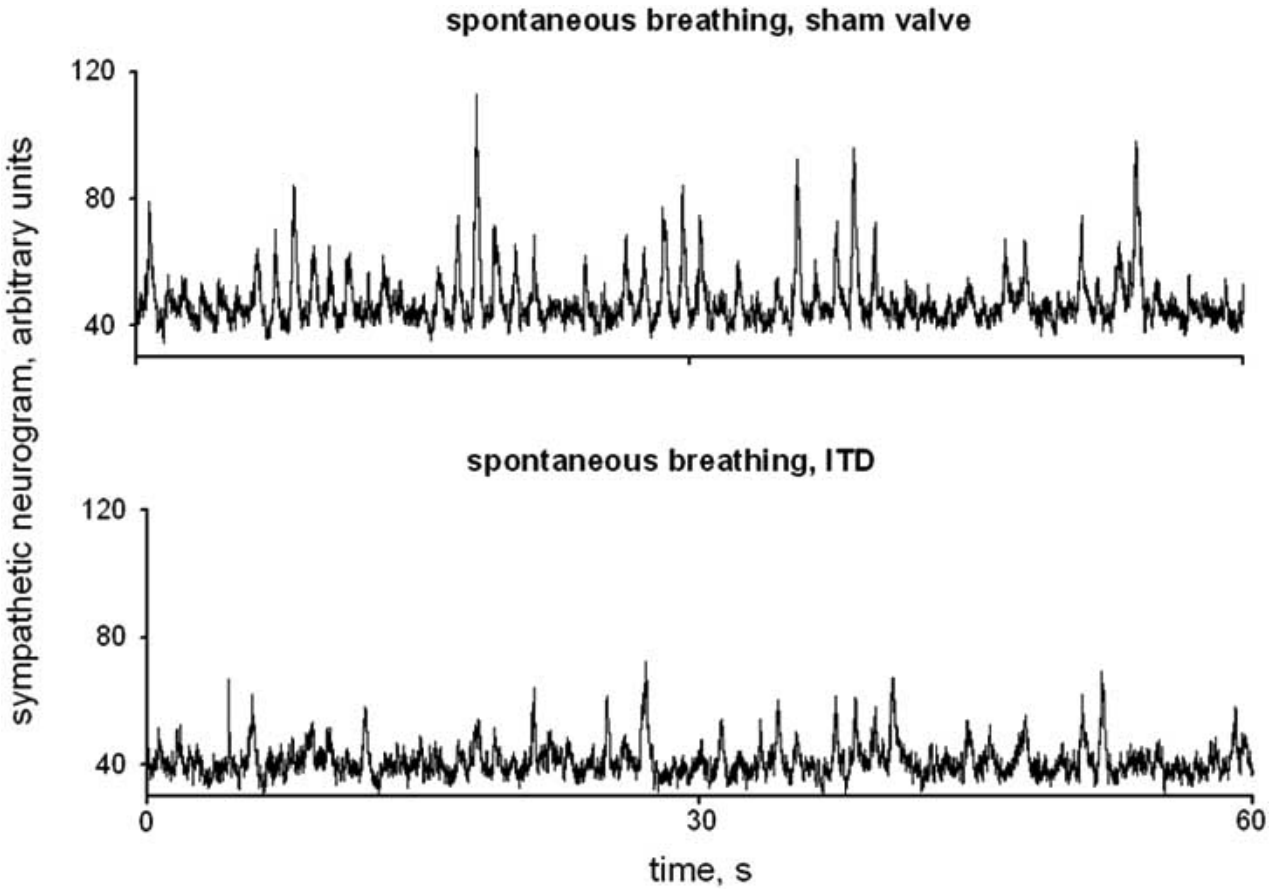

Fig. (6). Muscle sympathetic activity is shown for one subject breathing normally through a sham inspiratory impedance valve (0 cmH_2O) and an active inspiratory impedance valve (-7 cmH_2O). Figure reproduced from [96].

Standing upright with elevated stroke volume, cardiac output, and arterial pressure, in conjunction with lower peripheral resistance could conceivably improve orthostatic stability. To test the effectiveness of resistive breathing on orthostatic responses, subjects performed a "squat-stand test, " whereby they maintained a squatting position for 5 minutes while breathing through either a sham valve (0 cmH_2O inspiratory pressure) or an active valve (-7 cmH_2O inspiratory pressure) in a randomized, counterbalanced design (n = 18). Stroke volumes, arterial pressures, and cardiac outputs were better maintained during active ITD than sham ITD breathing when subjects moved from a squat to stand position. These data are shown in Fig. (**7**). For one subject, symptoms of severe presyncope during standing with the sham valve were resolved completely when he stood while breathing through the active valve. Sympathetic traffic was not measured, but mean peripheral vascular resistance was significantly lower when subjects stood while breathing through the active compared to the sham inspiratory valve.

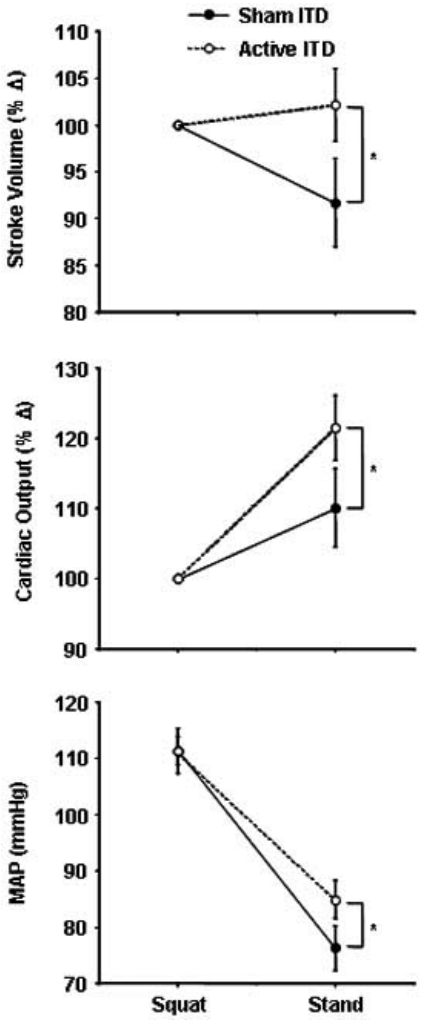

Fig. (7). Changes in stroke volume (upper panel), cardiac output (middle panel), and mean arterial blood pressure (lower panel) during spontaneous breathing on a sham (closed circles, solid lines) and active (open circles, broken lines) ITD. Circles and lines represent mean ± 1 standard error (n = 18); Data are unpublished observations from Convertino, V.A.

Orthostatic intolerance and syncope develop, ultimately, due to reduced cerebral oxygenation. We have shown in 7 subjects that breathing on the active ITD causes significant increases in mean cerebral blood flow velocity from 62 to 68 cm/s (p = 0.01) [Cooke, W.H. and Convertino, V.A. unpublished observations]. The effects of breathing through an active ITD on cerebral blood flow velocity are shown for one subject in Fig. (**8**). Elevated blood flow velocities persist throughout resistive breathing and then return to baseline with no change in arterial pressure upon cessation of resistive breathing as shown in Fig (**9**).

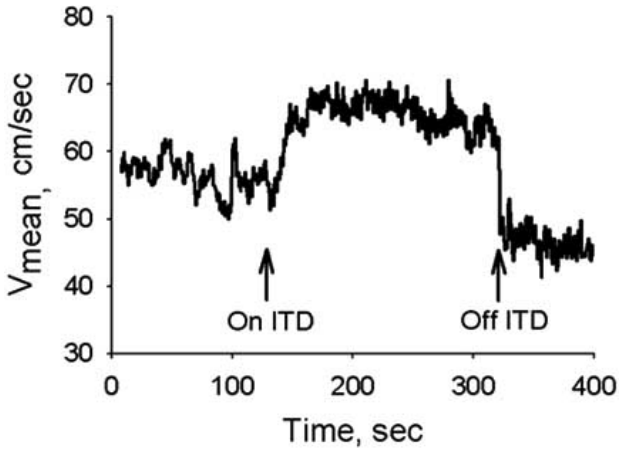

Fig. (8). Original data tracing from one subject showing the effects of breathing on the active inspiratory valve (-7 cmH_20) on mean cerebral blood flow velocity (V_{mean}); Data are unpublished observations from Cooke, W.H. and Convertino, V.A.

Our data and the data of others [93-102] suggest that the negative intrathoracic pressures induced by breathing through an active ITD generates a vacuum sufficient to draw blood toward the heart to increase systemic pressures and cerebral blood flow velocity. The combined increase of arterial pressure and cerebral blood flow velocity may be conducive to slowing or preventing progression to hemodynamic instability for astronauts following spaceflight or patients suffering syncopal attacks. In addition, such enhancement would also likely assist in the stabilization of bleeding patients awaiting more aggressive medical intervention.

Remote Triage

The most recent NASA Bioastronautics Critical Path Roadmap (BCPR) provides an approach to risk reduction and management for long duration human space flight. One of the primary areas for risk reduction and management is the development of an autonomous medical care system. This system would require the capability to provide medical care during a mission with little or no real-time support from Earth. This capability would have to include the ability of crew medical officers or other crewmembers to provide routine and emergency medical care using available resources in a remote situation. The local resources in the proposed autonomous system would have to be designed to augment and support the caregiver. Medical monitoring with specific physiological sensors will provide an effective means to as-

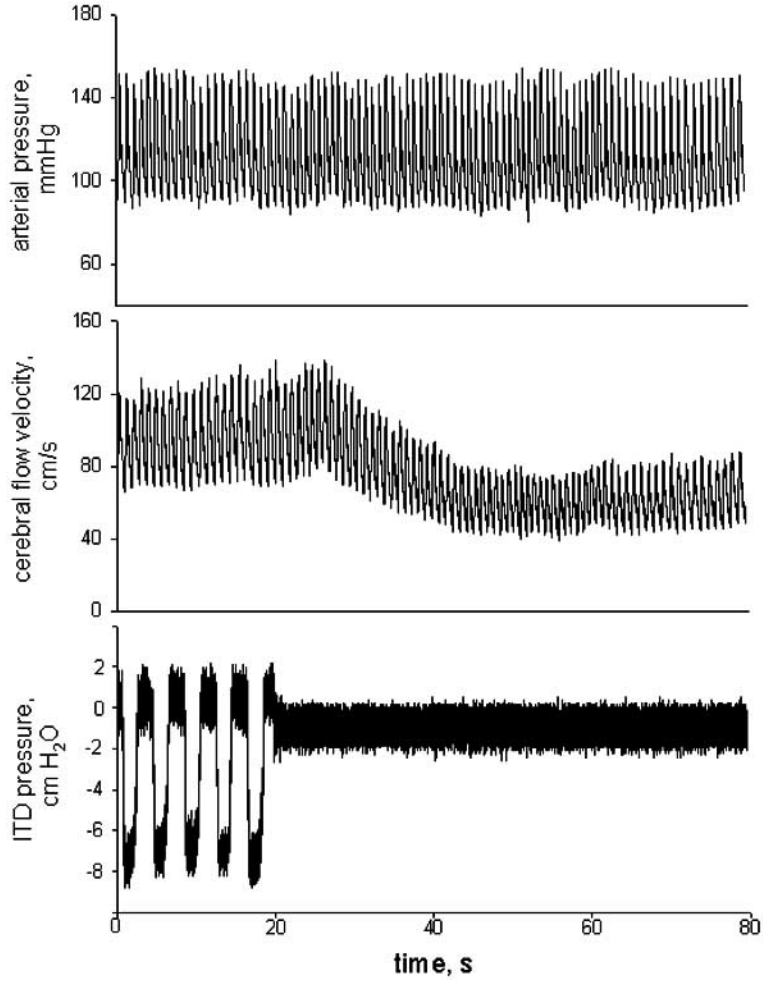

Fig. (9). Acute reduction of cerebral flow velocity upon removal of the active inspiratory valve (-7 cmH_20) shown in conjunction with arterial pressure for one subject; Data are unpublished observations from Cooke, W.H. and Convertino, V.A.

sess and/or identify clinical conditions that may require early treatment. There is a heightened risk of major illness or trauma that increases as the length of missions increase and activities become more physical (e.g. construction, vehicle driving). Lack of a capability to diagnose and/or treat major or minor illnesses and injuries can lead to more significant medical conditions that pose a threat to life and mission. Adequate monitoring, diagnosis, and treatment of a crewmember's illness or injury will be at risk without a capability to obtain, integrate and manage data, information, and knowledge in a continuous fashion. Finally, there is concern for the added risk of not having crewmembers with the appropriate medical skills and training to perform the medical procedures required for life saving care.

Like the remote separation of crewmembers during space missions, soldiers in the future battlefield environment will be widely dispersed, being separated by time and distance from medic or buddy aid as well as higher echelons of medical care. Like spaceflight, remote military operations place a requirement on an autonomous capability for treatment, stabilization, and maintenance of wounded soldiers with technology that provides moment-to-moment real-time monitoring of sensitive predictors for the onset of life threatening conditions and requirements for life saving interventions. Large gains can be achieved potentially for advancing the capabilities of combat medics by simplifying and improving initial assessment of battlefield injury, appropriate intervention, and priorities for early evacuation of combat casualties. The development of an autonomous medical care system similar to that outlined by the BCPR for extended space missions could prove helpful to advancing the capabilities of battlefield casualty care by combat medics.

With adaptations of the cardiovascular system in microgravity that compromise compensatory responses to low blood volume, the risk for development of circulatory shock from a traumatic injury during a space mission is increased. In this regard, it is possible that circulatory collapse or hemorrhagic shock may represent one of the more common life threatening conditions in space travel. Acute hemorrhage and subsequent circulatory collapse (shock) account for about 50% of the deaths on the battlefield, a statistic that has remained relatively unchanged since World War I [83]. Likewise, uncontrolled hemorrhage accounts for up to 82% of the early operative deaths from trauma in the civilian arena. However, the mortality rate in combat casualties drops to between 2% and 4% if the trauma patient is stabilized

through surgery [83]. It is therefore clear that the ability to significantly reduce adverse consequences of circulatory collapse in space, on the battlefield, or in civilian trauma will depend heavily on improving the capability for providing continuous monitoring for early diagnosis and treatment.

Optimal management designed to prevent the onset of circulatory shock requires a recognition and integration of multiple complex physiological responses with varying time courses. The resulting challenge is that shock is easily diagnosed in late stages when therapy is ineffective while early diagnosis is difficult in the absence of measurements that represent physiological responses associated with the underlying mechanisms of shock. The solution to this dilemma is to identify the physiologic signal(s) that provides the best *early* indicators of blood volume loss and impending circulatory collapse. Such requirements for complicated information and decision-making can overwhelm a physician well-trained in critical care medicine much less a first level responder (medic). Human capabilities for making the most appropriate and timely decisions for application of an effective life saving intervention can be augmented by new technologies that provide automated data mining, trending and decision support software. Previous efforts in this direction have centered upon developing hardware for casualty assessment. However, before developing hardware, an effective database of multiple physiologic signals associated with blood pressure regulation must be constructed and evaluated to identify the *best early* predictors of impending cardiovascular collapse. Development of the optimal hardware (medical monitoring devices) will depend on validating an algorithm that identifies primary predictive physiological signals. This algorithm should provide the medical care giver with essential, continuous information about the severity and clinical progression of the casualty and remote triage decision-making for prioritization of care and evacuation. Therefore, the result of space and military research in trauma care should enhance significantly the decision making capability of the medical care giver and subsequently improve clinical outcome.

The physiology of an individual suffering from cardiovascular collapse is dynamic, yet monitoring has traditionally been based on isolated measurements even under the best circumstances. The absence of frequent physiological measurements forces medical care givers to make rapid decisions about priority of care and application of interventions based upon isolated "snapshot" data points (e.g. blood pressure, pulse character, respiratory rate, mental status) without the benefit of observing trends and the dynamic nature of the evolving trauma physiology. Thus, the current process of care for cardiovascular compromise can be improved greatly by providing appropriate continuous physiological observations. In support of this concept, data from civilian trauma literature shows that temporal patterns of physiological responses during hemorrhage are more informative than single measurements because they provide a history of physiologic events that lead to shock [103]. It is therefore clear that identification of the best early predictors of circulatory collapse can only be accomplished by simultaneous and continuous measurement of various physiological signals (responses). Such an approach should be considered to be imperative in driving the development of autonomous medical monitoring systems for both astronauts and victims of trauma.

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